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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Pharmaceutical Preparations for the Oral Administration of Dihydropyridines in Beverage Form

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Abstract

Pharmaceutical preparations for the oral administration of dihydropyridines in beverage form are described. These preparations contain a coprecipitate of essentially amorphous dihydropyridine with a suitable pharmacologically acceptable polymer. The corresponding preparation processes are also described.

The present invention relates to pharmaceutical preparations for oral administration of dihydropyridines in beverage form.

The administration of pharmaceutical preparations based on dihydropyridines is a quite awkward problem, because of the extremely low solubility of these chemical compounds.

The method usually used to obtain an adequate bio-availability is based on the administration of these dihydropyridines in amorphous or micellar form. Nimodipine, nifedipine and nisoldipine are among the best-known representatives of dihydropyridines that are administered in this manner.

The amorphous state is customarily obtained by preparations of coprecipitates with pharmacologically acceptable polymers, such as polyvinylpyrrolidone (PVP), while the formation of micelles is customarily obtained by dilution of solutions which have high contents of surfactants and contain alcohols as auxiliaries.

A common problem in both cases is to prevent crystal formation processes. Crystal formation can dramatically affect the bioavailability of some dihydropyridines, among them nimodipine, since the solubilities of the amorphous and crystalline forms differ greatly.

Nimodipine is used for the treatment of inadequate cerebral circulation, on the part of elderly patients, who are the main group of possible patients. Among the various available pharmaceutical forms of nimodipine, the drop preparation has

remarkable and valuable advantages.

A weak point of the pharmaceutical drop pr paration, however, is the necessity that the patient must measure out (i.e. c unt) the drops himself. This apparently simple activity can actually be a considerable obstacle for an elderly patient and can be perceived as very arduous.

In one aspect, the present invention provides a pharmaceutical preparation, which comprises:

(i) an effective amount of a pharmaceutically active dihydropyridine in the form of a coprecipitate of essentially amorphous dihydropyridine with a water-soluble pharmacologically acceptable polymer, and

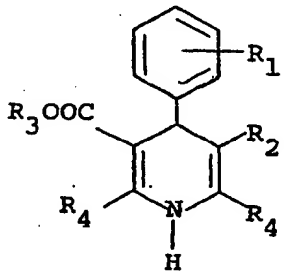
(ii) a beverage base,

wherein the pharmaceutical preparation is in a water-dispersible solid individual dose form and is adapted for being administered as a beverage by adding drinking water thereto prior to use.

Among the various possible solutions, one which has been found to be most suitable is to prepare a water-dispersible individual dose, which is adjusted organoleptically such that unpleasant taste of the active ingredient is masked by the beverage base. Dried fruit juices such as orange juice granules have proven very expedient for this purpose. Where desired, an appropriate flavor may also be added. The presence of an effervescent system (such as a combination of an edible solid acid and an edible carbonate) also contributes to the acceptability of the preparation and to the safe dispersion of the active

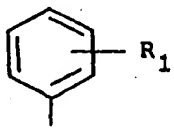
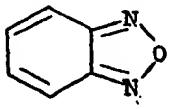
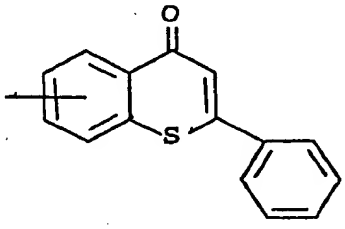
ingredient.

The dihydropyridines are generally well known in the art and the water-soluble pharmacologically acceptable polymers are also very well known. The dihydropyridines include those of the formula:



in which

R_1 stands for one or two identical or different substituents from the group comprising nitro, halogen, trifluoromethyl or $OCHF_2$ or in which

 stands for  or for 

R_2 stands for a nitro group or for the radical $COOR_6$, where

R_6 denotes alkyl having 1 to 19 C atoms which is optionally substituted by alkoxy having 1 to 4 carbon atoms or by one or more halogens,

or where

R_2 together with R_5 stands for the lactone group $-CO-O-CH_2-$,

R_3 stands for alkyl having 1 to 10 C atoms, which is optionally substituted by alkoxy having 1 to 4 C atoms or by one or more fluorines and R_4 and R_5 are identical or different and in each case stand for alkyl having 1 to 4 C atoms, which is optionally substituted by hydroxyl. A preferable dihydropyridine:polymer ratio (weight) from about 1:0.5 to 1:6. A preferred amount of the beverage base may be 5 to 200 mg per mg of the coprecipitate. The beverage base is preferably granules containing a sugar and dried fruit juice. Examples of the water-soluble pharmacologically acceptable polymers include polyvinylpyrrolidone, polyethylene glycol and polyethylene-polypropylene glycol block copolymer ("poloxamer").

The invention is further illustrated by reference to the accompanying drawings, of which:

Figure 1 is a graph showing the solution profile of effervescent granules containing amorphous nimodipine/PVP 25 coprecipitates, using coprecipitates with ratios of nimodipine to PVP 25 of 1:3, 1:2 and 1:1;

Figure 2 is a graph showing the solution profile of effervescent granules containing nimodipine/PVP 30 coprecipitates, using coprecipitates with ratios of nimodipine to PVP 30 of 1:3, 1:2 and 1:1;

Figure 3 is a graph showing the solution profile of effervescent granules containing nimodipine/PVP 90 coprecipitates,

using coprecipitates with ratios of nimodipine to PVP 90 of 1:2 and 1:1;

Figure 4 is a graph showing the solution profile of drops, effervescent granules and tablets containing nimodipine in 1.3 liter of 0.1N HCl stirred at 50 rpm; and

Figures 5 and 6 are each a table showing the results of stability tests of the preparation of Example 4.

In order to ensure the dissolution of the dihydropyridine, e.g. nimodipine, the nimodipine/PVP coprecipitate may preferably be employed in the formulation. The amount of PVP may be such that it is adequate for the safe retention of the amorphous state of the nimodipine without causing an undesired formation of foam during the effervescent activity.

The dihydropyridine/polymer coprecipitates can be prepared by various procedures. There are illustrated, referring to nimodipine and PVP by way of example, in the following.

- Dissolution of nimodipine (1 part) and PVP (3 parts) in an organic solvent, e.g. acetone (3 parts), with subsequent drying in an oven under reduced pressure.

- Atomisation of a solution of nimodipine and PVP in rganic solvent.

- Dissolution of nimodipine (1 part) and PVP 25 (M.W. about 25,000) (3 parts) in tetrahydrofuran (3 parts). Precipitation by means of petroleum benzine (7 parts). Filtration and drying of the coprecipitate.

- Drying of a solution of nimodipine and PVP in an organic solvent in a fluidised bed apparatus under reduced pressure.

- Freeze-drying of a solution of nimodipine and PVP in a suitable organic solvent, such as tert-butyl alcohol, etc.

The optimum nimodipine/PVP ratio was determined by investigation of the solution profile of an amount of coprecipitate equivalent to 15 mg of nimodipine, in the equipment known from the various pharmacopoeias and suitable for this.

The test conditions are:

Medium volume 1300 ml of 0.1N HCl

T^{o} = 37°C

Speed of the stirrer blade: 50 rpm.

The results obtained with the nimodipine/PVP 25 coprecipitate are represented in Figure 1. They confirm that there is a direct dependence of the amount of active ingredient which is released on the amount of PVP which is present in the coprecipitate. If the ratio 1:3 was used, a very satisfactory dissolution profile was obtained, an 80% dissolution being achieved after 15 minutes, which proved virtually stable for more than 2 hours.

The abovementioned values point to a supersaturation with a small, or even no, tendency for recrystallisation. Higher amounts of PVP are therefore superfluous from this point of view, while they could lead to an undesired superfluous formation of foam. According to the present invention, other types of PVP, such as e.g. PVP 30 (M.W. about 30,000) and PVP 90 (M.W. about 90,000), can also be employed.

In comparison to PVP 25, the results in Figure 2 show that with the ratio nimodipine:PVP 30 = 1:2 higher concentrations are obtained and with the ratio 1:3, on the other hand, no difference exists.

The coprecipitate obtained with PVP 90 is a third example. In this case, only coprecipitates with the ratio 1:1 or 1:2 were prepared, because with the ratio 1:3 an unusable plastic mass is obtained.

Using PVP 90, with the ratio 1:1 a good profile is obtained which appears to be unchangeable with the ratio 1:2.

The preferred polyvinylpyrrolidone according to the present invention is PVP 25; the preferred nimodipine:PVP ratio is 1:3.

As far as orange juice granules are concerned, they can be prepared with various concentrations by means of a fluidised bed granulator by spraying orange juice concentrate onto very fine sucrose. The effervescent substance pair was adjusted such that the finished beverage had a pH between 5 and 6, which is an optimum range for the retention of a pleasant taste with such preparations.

In the following, the invention is illustrated by some exemplary preparations based on pharmaceutically active dihydropyridines in effervescent granule form. In the examples, the parts are shown as parts by weight and the ratios as weight/weight data.

Example 1

Coprecipitate of nimodipine:PVP 25 (1:3)	120.0 mg
Citric acid	800.0 mg
Na bicarbonate	800.0 mg

Citrus flavouring	50.0 mg
Orange granules* q.s. to	3.5 g

* Exemplary composition of the orange granules:

Sucrose	1500.0 mg
Orange juice (dry)	200.0 mg
Saccharin sodium	7.0 mg
E 110	1.0 mg

Nimodipine and PVP 25 are dissolved in the ratio 1:3 in acetone (4 parts) at room temperature; the mixture is stirred until it is completely dissolved; after removal of the acetone by evaporation, the coprecipitate is obtained in the form of an amorphous brittle solid, which is then granulated and mixed with the other constituents.

Example 2

Coprecipitate of nimodipine:PVP 30 (1:2)	90.0 mg
Citric acid	800.0 mg
Na bicarbonate	800.0 mg
Citrus flavouring	50.0 mg
Orange granules* (see above) q.s. to	4.0 g

The procedure is as in Example 1.

Example 3

Coprecipitate of nifedipine:PVP 25 (1:3)	40.0 mg
Citric acid	800.0 mg
Na bicarbonate	800.0 mg
Citrus flavouring	50.0 mg
Orange granules* (see above) q.s. to	4.0 g

The procedure is as in Example 1.

Example 4

Coprecipitate of nisoldipine:PVP 25 (1:3)	40.0 mg
Citric acid	800.0 mg
Na bicarbonate	800.0 mg
Citrus flavouring	50.0 mg
Orange granules* (see above) q.s. to	3.5 g

The procedure is as in Example 1.

The results, which relate to the stability of the abovementioned preparations, are represented in Figures 5 and 6.

Example 5

Coprecipitate from nimodipine:PVP 25 (1:3)	120.0 mg
Citrus flavouring	50.0 mg
Lemon granules* (as above) p.s. to	5.0 g

The procedure is as in Example 1.

Example 6

Preparation of a coprecipitate by means of a fluidised bed granulator under reduced pressure.

Nimodipine (1 part) and PVP 25 (3 parts) are dissolved in acetone (8 parts) at room temperature; the mixture is stirred until it is completely dissolved; the solution is then spray-dried under the following conditions in a fluidised bed apparatus under reduced pressure with recovery of the solvent:

Inlet temperature	120°-150°C
- Outlet temperature	50°- 80°C
Spray throughput	1-1.5 kg/min

Example 7

Preparation of a coprecipitate by freeze-drying.

Nimodipine (5 parts) and PVP 25 (15 parts) are dissolved in tert-butyl alcohol (80 parts). The batch is then frozen at -10°C to -20°C and lyophilised according to customary processes.

Primary drying: gradual warming to +20°C.

Secondary drying: 4-5 hours at +40°C.

Example 8

Coprecipitate of nimodipine:poloxamer 407 (1:3)		120.0 mg
E 110 (the European color number for the food dyestuff Sunset Yellow)		1.0 mg
Saccharin		7.0 mg
Citrus flavouring		50.0 mg
Sucrose	q.s. to	3.5 g

The nimodipine/poloxamer F 127 (1:3) coprecipitate is dissolved in acetone (5 parts); the solution obtained in this way is employed for the granulation of very fine sucrose (22.5 parts). The mixture is screened and dried under reduced pressure.

The residue is granulated and mixed with further sucrose and citrus flavouring.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutical preparation, which comprises:

(i) an effective amount of a pharmaceutically active dihydropyridine in the form of a coprecipitate of essentially amorphous dihydropyridine with a water-soluble pharmacologically acceptable polymer, and

(ii) a beverage base,

wherein the pharmaceutical preparation is in a water-dispersible solid individual dose form and is adapted for being administered as a beverage by adding drinking water thereto prior to use.

2. A pharmaceutical preparation according to Claim 1, wherein the therapeutically active dihydropyridine is nimodipine, nifedipine or nisoldipine.

3. A pharmaceutical preparation according to Claim 1, wherein the pharmacologically acceptable polymer is polyvinylpyrrolidone, polyethylene glycol or polyethylene-polypropylene glycol block copolymer.

4. A pharmaceutical preparation according to Claim 1, wherein the pharmacologically acceptable polymer is polyvinylpyrrolidone having a molecular weight between 25,000 and 90,000 daltons.

5. A pharmaceutical preparation according to any one of Claims 1 to 4, wherein the dihydropyridine/polyvinylpyrrolidone weight ratio is between 1:2 and 1:5.

6. A pharmaceutical preparation according to Claim 1, having the following composition:

coprecipitate of nimodipine:		
polyvinylpyrrolidone (1:3)		about 120 mg
citric acid		about 800 mg
sodium bicarbonate		about 800 mg
citrus flavouring		about 50 mg
orange granules	q.s. to	about 3.5 g.

7. A pharmaceutical preparation according to any one of Claims 1 to 4, wherein the beverage base is dried fruit juice.

8. A pharmaceutical preparation according to Claim 7, wherein the dried fruit juice is in the form of granules containing a sugar and the dried fruit juice.

9. A pharmaceutical preparation according to any one of Claims 1 to 4, further comprising ingredients which together form an effervescent system.

10. A process for the production of the pharmaceutical preparation as defined in Claim 1, which comprises:

coprecipitating the dihydropyridine and the

pharmacologically acceptable polymer such that the dihydropyridine is obtained in an essentially amorphous form coprecipitated with the polymer, and

admixing the coprecipitate with the beverage base.

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Fig.1

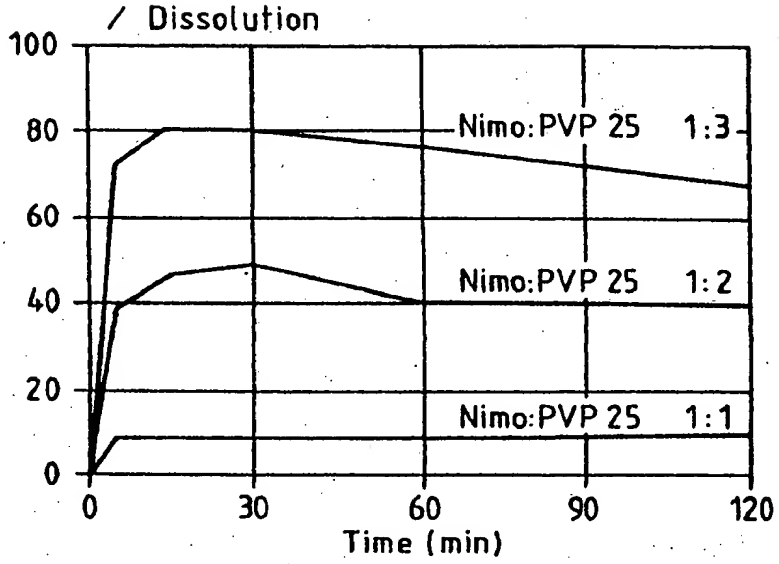

Fig.2

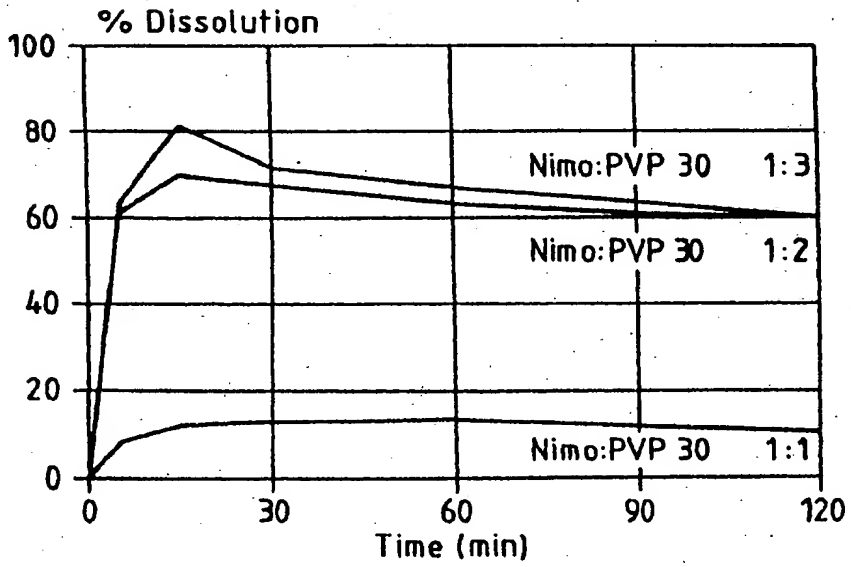

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Fig. 3

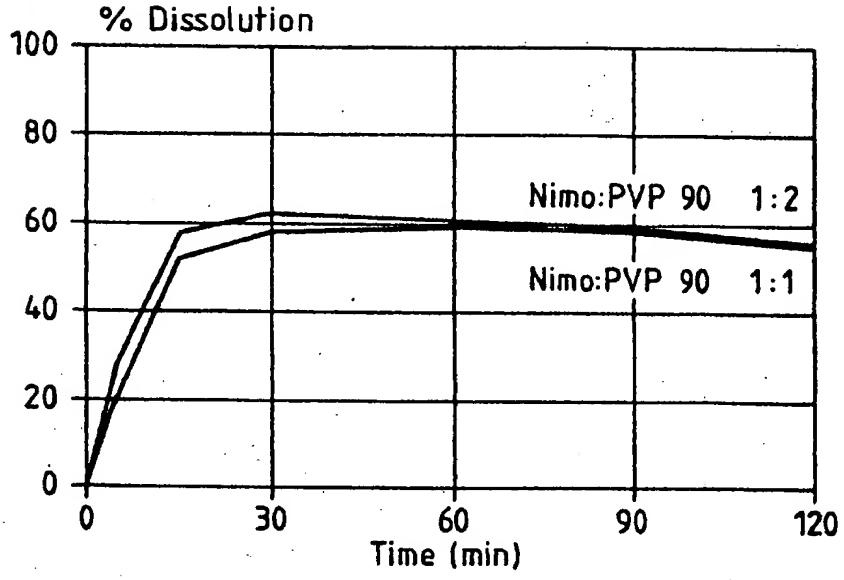

Fig. 4

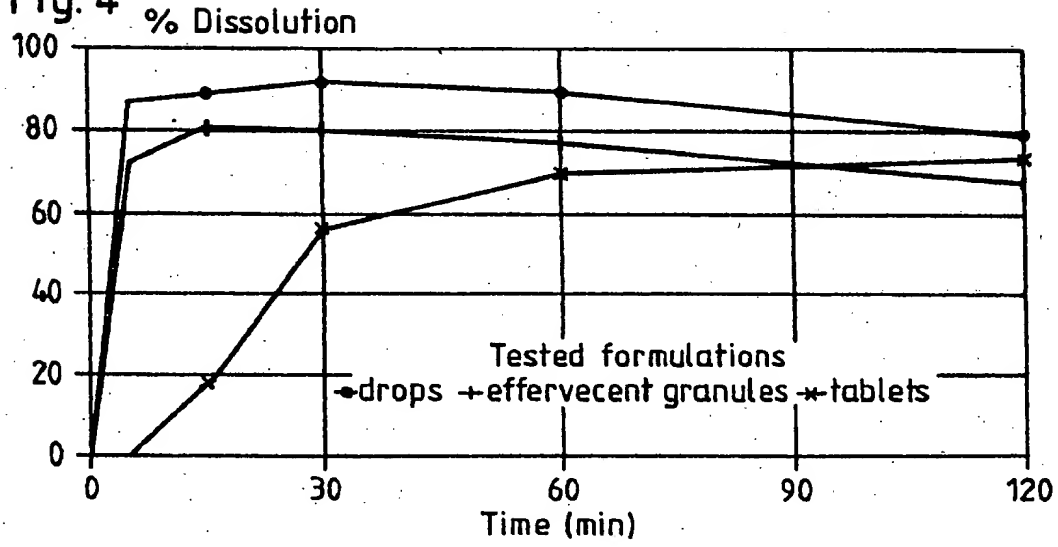

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Fig. 5

Test	T = 0	25°C	30°C	40°C
Appearance	unchanged	unchanged	unchanged	unchanged
pH	5,26	5,29	5,42	5,38
Solution test after 30'	80,5%	78,55%	81,5%	85,2%
Degradation products	not measurable	not measurable	not measurable	0,43%
Content mg/individual dose	30,8	30,5	30,6	30,4

Fig. 6

Test	T = 0	25°C	30°C	40°C
Appearance	unchanged	unchanged	unchanged	unchanged
pH	5,33	5,32	5,29	5,30
Solution test after 30'	81,2%	75,6%	76,8%	82,7%
Degradation products	not measurable	not measurable	not measurable	0,30%
Content mg/individual dose	30,3	30,9	30,7	30,3

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